REMARKS

Claims 14-16 and 18-26 are pending.

The specification is amended at paragraph [0004] to correct minor typographical errors and at [0069] to remove references to urls.

Claim 14 is amended to recite that the transgenic mouse comprises a deletion of the CIRL3-L gene and exhibits at least one diagnostic criterion for a psychiatric disorder that is an anxiety-related disorder selected from Asperger's syndrome, autism, and pervasive developmental disorder-not otherwise specified (PDD-NOS).

Claims 15-26 are canceled.

New claims 27-32 are added. New claims 27 and 28 recite the transgenic mouse of claim 14 exhibiting at least one or at least two, respectively, diagnostic criteria for Asperger's syndrome. New claims 29 and 30 recite the transgenic mouse of claim 14 exhibiting at least one or at least two, respectively, diagnostic criteria for autism. New claims 31 and 32 recite the transgenic mouse of claim 14 exhibiting at least one or at least two, respectively, diagnostic criteria for pervasive developmental disorder-not otherwise specified (PDD-NOS).

Support for the amendments to the specification and claims can be found in the specification and claims as filed. For example, support for the amendment to claim 14, and for new claims 27-33, can be found in claims 11-17 as filed and paragraphs [0005], [0008], [0014], and [0015] and in Figs. 1-4. Further support for the amendment to claim 14 (knockout of the CIRL3-L gene) can be found, for example, at paragraphs [0061] and [0071]. The amendments to the claims add no new matter, and the Examiner is respectfully requested to enter them.

I. Objection to the Specification

The Examiner objected to the specification as including an embedded hyperlink and/or other form of browser-executable code at paragraph [0069].

Applicants have deleted the urls that were cited at paragraph [0069]. Applicants submit that the amendment to the specification fully addresses the Examiner's objection.

II. Rejections under 35 USC § 101

The Examiner rejected claims 14-16 and 18-26 as allegedly lacking a specific, substantial and credible, or well-established utility. The Examiner asserted that the specification does not assert any utility for the claimed transgenic mouse, does not disclose a specific phenotype associated with any disease condition for the mouse, does not disclose any specific

or substantial utility for the mouse as a model or its use in a method of identifying compounds that modulate CIRL3-L, and that a person of ordinary skill would not have recognized a utility because the specification allegedly provides no correlation between a CIRL3-like gene and an established function, phenotype, or disease. The Examiner asserted that the specification discloses no function of a CIRL3-L gene in normal physiology or a known pathological state.

Applicants submit that the claim amendments and cancellations moot the Examiner's rejection. To the extent that the rejection might be applicable to the pending claims, Applicants address the question of utility in connection with the pending claims.

The pending claims satisfy the utility requirement. The claimed invention has a specific and a substantial utility. A specific utility is specific to the subject matter claimed, in contrast with a general utility that is applicable to the broad class of the invention. A substantial utility is one that defines a real world use, which does not require carrying out further research to identify or reasonably confirm a real world context.

The claimed transgenic mouse has utility as a mouse model of a psychiatric disorder, for example, a psychiatric disorder selected from Asperger's syndrome, autism, and pervasive developmental disorder-not otherwise specified (PDD-NOS). Applicants submit that it would be apparent from the disclosure to a person of ordinary skill in the art that the claimed transgenic mouse has utility as a mouse model of a human psychiatric disorder such as, for example, at least one of the recited psychiatric disorders.

In support of Applicants' argument that the specific and substantial utility would be readily apparent to a person of the ordinary skill, Applicants refer the Examiner to the specification, for example, at paragraphs [0008], [0014]-[0019], and in the figures, for example, Figs. 1B-D and Figs. 4A-B. A person of ordinary skill would recognize that the social interaction tests of Fig. 1, and the Open Field, Light/Dark Exploration, and Elevated Plus Maze tests are standard tests in the art employed to assess diagnostic indicators of the psychiatric disorders recited in the claims. Therefore, a person of ordinary skill in the art would readily recognize that the transgenic mouse exhibits one or more diagnostic criteria (as reflected in the assessment tests shown in the figures) of the recited psychiatric disorders. A person of ordinary skill would also recognize that the transgenic mouse exhibiting the diagnostic indicators would be useful to gauge the effectiveness of therapeutic interventions (including, but not limited to, pharmaceutical interventions) in the animal model.

A person of ordinary skill would also realize the value (*i.e.*, utility) of having an animal model of a psychiatric disorder such as, for example, autism, Asperger's syndrome, or PDD-NOS. Applicants submit that there is a dire need for animal models of such disorders, since

pharmacological therapeutics must otherwise be tested directly in humans, for example, children affected with one or more of the recited disorders. Because such testing is generally unethical, new and useful pharmacological interventions for the recited disorders must rely, typically, on either (1) serendipitous observations of therapeutics administered to affected persons for other indications, where the therapeutic is observed to exert a side-effect that is beneficial in treating the recited disorder, or (2) off-label usage. Thus, an animal model of the recited disorders has a specific and substantial utility as an animal model in which to test new indications of existing therapeutics, as well as new therapeutics, for efficacy as against the recited psychiatric conditions. Applicants refer the Examiner to Fig. 5, which illustrates using a diagnostic test (Latency to Groom/Number of Grooms) to assess the efficacy of a psychoactive therapeutic (imipramine) on normal and CIRL3-L knockout mice. A person of ordinary skill would recognize, for example, that number of grooms would correlate with stereotyped or repetitive behavior (which is a diagnostic criterion for, for example, Asperger's syndrome, according to the Diagnostic and Statistical Manual for Mental Disorders IV (DSM-IV); see DSM-IV at 299.80(C)).

It would be apparent from the specification as filed, to a person of ordinary skill in the art, that the claimed transgenic mouse would have a specific and a substantial utility as an animal model for screening medications useful for autism. A person of ordinary skill would recognize from the specification that the claimed mouse could be used to assess efficacy of medications now being tested against certain developmental disorders. For example, tricyclics, such as imiprimine, antipsychotics, such as resipridone, stimulants, such as methylphenidate, and SSRIs, such as fluoxetine, have been or are being tested in developmental disorders related to autism. As shown in the specification, the claimed mice display developmental phenotypes that can be used as diagnostic indicators as measured by certain test protocols administered with or without the therapeutics (e.g., Fig. 1: social indicators; Fig. 2: motoric indicators; Fig. 3: sensory indicators; and Fig. 4: stereotypy and anxiety indicators).

Accordingly, Applicants request that the utility rejection be withdrawn.

III. Rejections under 35 USC §112, first paragraph: Written Description

The Examiner rejected claims 15, 16, 18, 19, and 21-23, as allegedly failing to satisfy the written description requirement. The Examiner asserted that the specification does not provide support for "perseverative developmental disability (PDD)."

Applicants have canceled claims 15-26 and submit that cancellation of the claims moots the Examiner's rejection. None of the amended claims or new claims recite the phrase "perseverative developmental disability."

IV. Rejections under 35 USC §112, first paragraph: Enablement

The Examiner rejected claims 14-16 and 18-26 as allegedly not enabled. The Examiner asserted that producing a transgenic mouse comprising a homozygous disruption in endogenous CIRL-3L gene, and producing a transgenic mouse comprising a human CIRL-3L gene, wherein the mouse exhibits anxiety-related disorders, requires undue experimentation. The Examiner asserted that the data in the specification "does not disclose a coherent picture" (Office Action, page 14) of the function of the CIRL-3L gene or any condition associated with a CIRL-3L knockout, or any phenotype for a mouse having a human CIRL-3L gene. The Examiner asserted that expected phenotypes of knockout mice are not always observed, citing phenomena such as "hitchhiking alleles," "modifier genes," phenotype masking, and the influence of genetic background as confounding elements in identifying phenotypes (Office Action, pages 14-18).

Regarding claims 20-24, the Examiner asserted that the specification provides no guidance as to how a CIRL-3L gene would be expressed in a mouse, including the possibility of DNA methylation or deletion from the genome, a description of the elements of the construct used to make the transgenic animal, the effect of surrounding chromatin on a transgene, positional effects of random integration, and promoter selection. The Examiner asserted that it would require undue experimentation to establish levels of transgene product and the phenotype of the product since the specification allegedly lacks guidance to overcome the unpredictabilities of successfully making a transgenic mouse with a specific anxiety-related disorder phenotype.

Regarding claims 25-26, the Examiner asserted that the specification provides no guidance for identifying an agent capable of reducing anxiety in a mammal by administering a test agent to the transgenic animal of the invention. The Examiner asserted that the specification lacks guidance that would relate CIRL-3L's function to an anxiety related disorder, and does not disclose a relationship of CIRL-3L to an anxiety-related condition that could be treated by an agent identified by the claimed methods. A person of ordinary skill would allegedly not know the function of CIRL-3L, would be unaware of any relationship of CIRL-3L to any disease or condition, and would have to ascertain the function of CIRL-3L. Undue experimentation would be required to establish a link between CIRL-3L and the phenotype of

the transgenic animal, then to test various parameters using different agents and dosages and delivery routes in order to reduce symptoms observed in the transgenic animal.

Applicants submit that the Examiner's rejections are moot in light of the amendment to claim 14 and cancellation of claims 15-26. Applicants will address the Examiner's observations regarding enablement as they might be applied to amended claim 14 and new claims 27-32.

Amended claim 14 and new claims 27-32 are enabled by the specification. No undue experimentation is required to practice the invention as presently claimed. Applicants submit that the phenotype of the claimed CIRL3-L transgenic mouse is apparent to a person of ordinary skill in the art in light of the specification, and that the specification does not fail to disclose a "coherent picture" of CIRL3-L function.

Applicants claim a CIRL3-L knockout mouse wherein the mouse exhibits at least one diagnostic criterion of a psychiatric disorder that is an anxiety-related disorder selected from OCD, Asperger's syndrome, autism, and PDD-NOS. A person of ordinary skill, in light of the specification and knowledge in the art, would recognize that the disclosed phenotype of the CIRL3-L knockout mouse correlates well with diagnostic criteria set forth in the DSM-IV for the recited disorders. See, e.g., DSM-IV at 299.00 (diagnostic criteria for autistic disorder), 299.80 (diagnostic criteria for Asperger's disorder), and 299.80 (diagnostic criteria for PDD-NOS). The specification describes that the CIRL3-L knockout mouse displays one or more phenotypes that correlate with diagnostic criteria for one or more of the diagnostic criteria of the recited disorders, as reflected by, for example, the data of Figs. 1-5. Thus, no undue experimentation is required to arrive at a phenotype for the recited CIRL3-L knockout mouse.

The diagnostic criteria in the DSM-IV for autism are reproduced below:

Diagnostic Criteria for 299.00 Autistic Disorder

(A) A total of six (or more) items from (1), (2), and (3), with at least two from (1), and one each from (2) and (3):

(1) qualitative impairment in social interaction, as manifested by at least two of the following:

(a) marked impairment in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction

(b) failure to develop peer relationships appropriate to developmental level

(c) a lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing, or pointing out objects of interest)

(d) lack of social or emotional reciprocity

(2) qualitative impairments in communication as manifested by at least one of the following:

delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime)

(a) in individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others
(b) stereotyped and repetitive use of language or idiosyncratic language
(c) lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level

(3) restricted repetitive and stereotyped patterns of behavior, interests, and activities, as manifested by at least one of the following:
encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
(a) apparently inflexible adherence to specific, nonfunctional routines or rituals
(b) stereotyped and repetitive motor manners (e.g., hand or finger flapping or twisting, or complex whole-body movements)
(c) persistent preoccupation with parts of objects

(B) Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years: (1) social interaction, (2) language as used in social communication, or (3) symbolic or imaginative play.

(C) The disturbance is not better accounted for by Rett's Disorder or Childhood Disintegrative Disorder.

The claimed mouse meets at least two out of three of the DSM-IV's criteria for autistic disorder. For example, Fig. 1D establishes that the claimed mouse exhibits behavior that meets diagnostic criterion 299.00(A)(1); Figs. 4A-B establish that the claimed mouse meets diagnostic criterion 299.00(A)(3). The third diagnostic criterion of autism, 200.00(2) (delays in spoken language) are not correlatable in a mouse model. Fig. 1D shows impairment in face to body postures (see DSM-IV 299.00(A)(1)(a)), failure to develop appropriate peer relationships (DSM-IV 299.00(A)(1)(b)) and the specification at paragraph [0073] recites consistent abnormal social patterns (DSM-IV 299.00(B)(1)); Fig. 4A-B shows stereotyped and repetitive motor patterns (DSM-IV 299.00(3)(b)). None of the mouse's disturbances could be accounted for by Rett's disorder or Childhood Disintegrative Disorder (DSM-IV 299.00(C)). Thus, the claimed transgenic mouse meets at least some of the DSM-IV diagnostic criteria for autism. Accordingly, a person of ordinary skill in the art would recognize autism as a phenotype of the claimed transgenic mouse.

Similarly, the claimed mouse meets at least a required two out of the five diagnostic criteria for Asperger's disorder as set forth in the DSM-IV (see, DSM-IV at 299.80(A) through (F)). The DSM-IV diagnostic criteria for Asperger's disorder are reproduced below:

Diagnostic Criteria for 299.80 Asperger's Disorder

(A). Qualitative impairment in social interaction, as manifested by at least two of the following:
(1) marked impairment in the use of multiple nonverbal behaviors such as eye-to eye gaze, facial expression, body postures, and gestures to regulate social interaction
(2) failure to develop peer relationships appropriate to developmental level

(3) a lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing, or pointing out objects of interest to other people)
(4) lack of social or emotional reciprocity
(B) Restricted repetitive and stereotyped patterns of behavior, interests and activities, as manifested by at least one of the following:
(1) encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity of focus
(2) apparently inflexible adherence to specific, nonfunctional routines or rituals
(3) stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting, or complex whole-body movements)
(4) persistent preoccupation with parts of objects
(C) The disturbance causes clinically significant impairment in social, occupational, or other important areas of functioning.
(D) There is no clinically significant general delay in language (e.g., single words used by age 2 years, communicative phrases used by age 3 years).
(E) There is no clinically significant delay in cognitive development or in the development of age-appropriate self-help skills, adaptive behavior (other than in social interaction), and curiosity about the environment in childhood.
(F) Criteria are not met for another specific Pervasive Developmental Disorder or Schizophrenia.

The claimed transgenic mice show marked impairment in using multiple nonverbal behaviors, including body postures and gestures to regulate social interaction (DSM-IV 299.80(A)(1); Figs. 1B-D); the mice fail to develop appropriate peer relationships (DSM-IV 299.80(A)(2); Figs. 1B-D); the mice lack social reciprocity (DSM-IV 299.80(A)(4); the mice exhibit stereotyped and repetitive motor mannerisms (DSM-IV 299.80(B)(3); Figs. 4A-B); the mice display significant impairment in social functioning (DSM-IV 299.80(C); Figs. 1B-D); and there is no apparent significant delay in cognitive development (DSM-IV 299.00(E).)). Thus, the claimed transgenic mouse meets at least some of the DSM-IV diagnostic criteria for Asperger's syndrome. Accordingly, a person of ordinary skill in the art would recognize Asperger's syndrome as a phenotype of the claimed transgenic mouse.

Similarly, the claimed mouse meets the diagnostic criteria for pervasive developmental disorder-not otherwise specified (PDD-NOS) as set forth in the DSM-IV (see, DSM-IV at 299.80 PDD-NOS). The DSM-IV diagnostic criteria for PDD-NOS are reproduced below:

299.80 Pervasive Developmental Disorder Not Otherwise Specified (Including Atypical Autism)

This category should be used when there is a severe and pervasive impairment in the development of reciprocal social interaction associated with impairment in either verbal or nonverbal communication skills or with the presence of stereotyped behavior, interests, and activities, but the criteria are not met for a specific Pervasive Developmental Disorder, Schizophrenia, Schizotypal Personality Disorder, or Avoidant

> Personality Disorder. For example, this category includes "atypical autism" - presentations that do not meet the criteria for Autistic Disorder because of late age at onset, atypical symptomatology, or subthreshold symptomatology, or all of these.

The claimed transgenic mice exhibit the severe and pervasive impairment in the development of reciprocal social interaction associated with impairment in nonverbal communication skills, with the presence of stereotyped behavior (reflected in the figures and at paragraphs [0072] through [0077] of the specification as filed), where the criteria are not met for other specified disorders. Thus, the claimed transgenic mouse meets the DSM-IV diagnostic criteria for PDD-NOS. Accordingly, a person of ordinary skill in the art would recognize PDD-NOS as a phenotype of the claimed transgenic mouse.

Applicants submit that it is of no moment that the phenotype of the claimed mouse encompasses Asperger's syndrome, autism, and/or PDD-NOS. A person of ordinary skill would recognize that the phenotypes in humans of these disorders can overlap to some extent. Thus, observation of such overlap in the claimed transgenic mouse is a reflection of the phenotype in man.

Applicants submit that some variance in phenotypical severity across mouse background is of no moment with respect to enablement regarding the claimed transgenic mouse, since any alleged variances in phenotype as the result of genetic background may also occur in man. But regardless of the presence or absence of some variance, the claimed mice match one or more of the diagnostic criteria for the disorders recited in the claims.

In light of the above, Applicants submit that the claimed transgenic mouse if fully enabled by the specification.

V. Rejections under 35 USC §112, second paragraph: Indefiniteness

The Examiner rejected claims 14-16 and 18-26 as allegedly indefinite for citing an altered or deleted endogenous CIRL-3L gene because the claim does not specify whether it encompasses mice with no CIRL-3L gene, mice with disruptions in the CIRL-3L gene that express a nonfunctional protein, or mice with disruptions in the CIRL-3L gene that express a partially functional protein. The Examiner also asserted that the phrase "characterized by" renders claim 14 indefinite for lack of clarity as to whether the claim is limited to a phenotype of an anxiety-related disorder or whether the claim is limited to how the mouse is tested for an anxiety-related disorder.

Claim 14 has been amended to recite that the transgenic mouse comprises a deleted CIRL3-L gene (*i.e.*, a knockout of CIRL3-L). Claims 15-26 have been canceled. Applicants

submit that the amendment to claim 14 and the cancellation of claims 15-26 moot the Examiner's indefiniteness rejection.

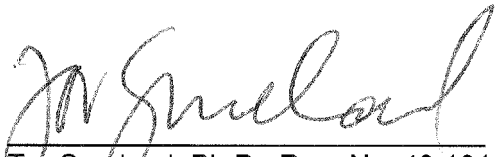
Conclusion

It is believed that this document is fully responsive to the Office Action dated 09 January 2007. It is believed that the claims are in condition for allowance, and such action is respectfully urged.

Fees

No fee other than the fee for a one-month extension of time is believed to be due in connection with filing this response. The Commissioner is hereby authorized to charge Deposit Account Number 18-0650 in the amount of $120.00 for a one-month extension of time. If any further or other fees are deemed due, or overpayments have been made, the Commissioner is hereby authorized to charge, or credit, Deposit Account Number 18-0650 for any fees due or overpayments made.

Respectfully submitted



Tor Smeland, Ph.D., Reg. No. 43,131
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, New York 10591
(914) 345-7435 (direct)